

12

EUROPEAN PATENT APPLICATION

21 Application number: **89305083.1**

51 Int. Cl.4: **C07D 403/06 , A61K 31/415 , C07C 119/12**

22 Date of filing: **19.05.89**

Claims for the following Contracting States: ES
+ GR.

30 Priority: **20.05.88 GB 8812002**

43 Date of publication of application:
13.12.89 Bulletin 89/50

84 Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

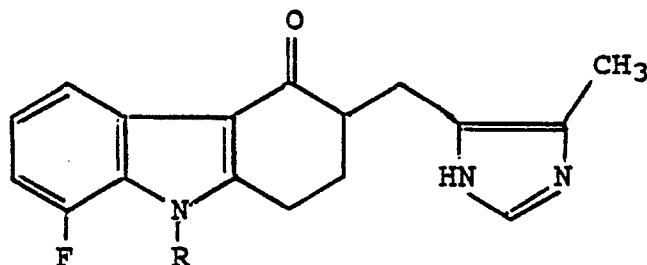
71 Applicant: **GLAXO GROUP LIMITED**
Clarges House 6-12 Clarges Street
London W1Y 8DH(GB)

72 Inventor: **Price, Barry John**
5 Cowpers Way
Tewin Wood Hertfordshire(GB)
Inventor: **Coates, Ian Harold**
20 Mandeville Road
Hertford Hertfordshire(GB)
Inventor: **Bradshaw, John**
1 Putty Hall Cottages Shaftenhoe End
Barley Royston Hertfordshire(GB)
Inventor: **Mitchell, William Leonard**
230 Barker Drive
London, NW1 0JF(GB)

74 Representative: **Marchant, James Ian et al**
Elkington and Fife Beacon House 113
Kingsway
London WC2B 6PP(GB)

54 **Tricyclic ketones.**

57 The invention relates to tricyclic ketones of the general formula (I)



(I)

wherein R represents a hydrogen atom or a C₁₋₃alkyl group and physiologically acceptable salts and solvates thereof.

The compounds are potent and selective antagonists of the effect of 5-HT at 5-HT₃ receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

EP 0 345 956 A1

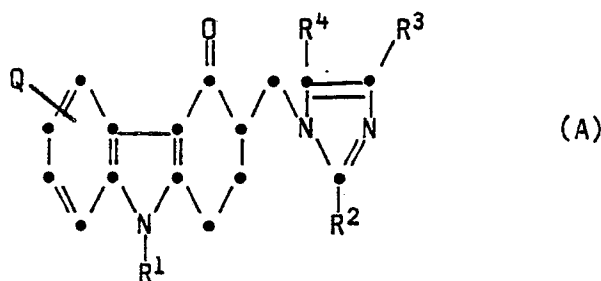
TRICYCLIC KETONES

This invention relates to tricyclic ketones, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

In particular the invention relates to compounds which are potent and selective antagonists of 5-hydroxytryptamine (5-HT) at 5-HT receptors of the type located on terminals of primary afferent nerves. Receptors of this type are now designated as 5-HT₃ receptors and are also present in the central nervous system. 5-HT occurs widely in the neuronal pathways in the central nervous system and disturbance of these 5-HT containing pathways is known to alter behavioural syndromes such as mood, psychomotor activity, appetite and memory.

Compounds having antagonist activity at 5-HT₃ receptors have been described previously.

Thus for example published UK Patent Specification No. 2153821A and published European Patent Specifications Nos. 191562, 219193 and 210840 disclose 3-imidazolylmethyltetrahydrocarbazolones which may be represented by the general formula (A):

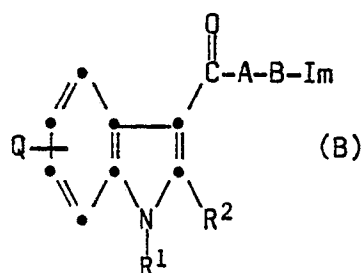


wherein R¹ represents a hydrogen atom or a group selected from C₁₋₁₀alkyl, C₃₋₆alkenyl, C₃₋₁₀alkynyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, phenyl or phenylC₁₋₃alkyl, and in the case where Q represents a hydrogen atom, R¹ may also represent -CO₂R⁵, -COR⁵, -ONR⁵R⁶ or -SO₂R⁵ (wherein R⁵ and R⁶, which may be the same or different, each represents a hydrogen atom, a C₁₋₆alkyl or C₃₋₇cycloalkyl group, or a phenyl or phenylC₁₋₄alkyl group, in which the phenyl group is optionally substituted by one or more C₁₋₄alkyl, C₁₋₄alkoxy or hydroxy groups or halogen atoms, with the proviso that R⁵ does not represent a hydrogen atom when R¹ represents a group -CO₂R⁵ or -SO₂R⁵);

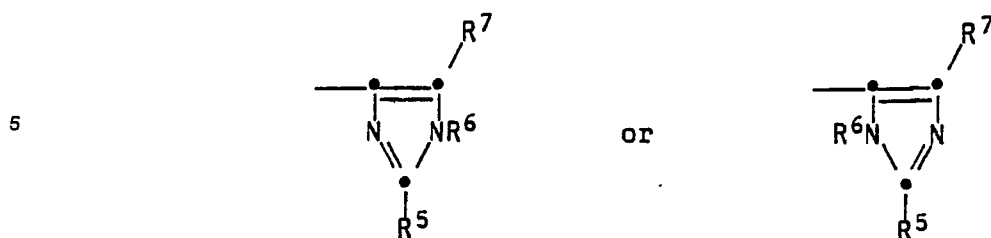
one of the groups represented by R², R³ and R⁴ is a hydrogen atom or a C₁₋₆alkyl, C₃₋₇cycloalkyl, C₂₋₆alkenyl, or phenylC₁₋₃alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆alkyl group; a represents a hydrogen atom or a halogen atom or a hydroxy, C₁₋₄alkoxy, phenylC₁₋₃alkoxy or C₁₋₆alkyl group or a group -N⁷R⁸ or -CONR⁷R⁸ - (wherein R⁷ and R⁸, which may be the same or different, each represents a hydrogen atom or a C₁₋₄alkyl or C₃₋₄alkenyl group, or together with the nitrogen atom to which they are attached form a saturated 5 to 7 membered ring);

and physiologically acceptable salts and solvates thereof.

Furthermore, published European Patent Specification No. 242973 discloses ketone derivatives which may be represented by the general formula (B):



wherein Im represents an imidazolyl group of formula:



Q represents a hydrogen atom;

R¹ represents a hydrogen atom or a C₁₋₆ alkyl, C₃₋₆ alkenyl,

C₃₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₄ alkyl, phenyl or phenylC₁₋₃ alkyl group;

15 R₂ represents a hydrogen atom or a C₁₋₆ alkyl, C₃₋₆ alkenyl, C₃₋₇ cycloalkyl, phenyl or phenylC₁₋₃ alkyl group;

A-B represents the group R³R⁴C-CH₂ or R³C=CH;

R³ and R⁴, which may be the same or different, each represents a hydrogen atom or a C₁₋₆ alkyl group;

20 one of the groups represented by R⁵, R⁶ and R⁷, is a hydrogen atom or a C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, phenyl or phenylC₁₋₃ alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆ alkyl group;

and physiologically acceptable salts and solvates thereof.

Published European Patent Specification No. 266899 discloses ketone derivatives which may also be represented by the general formula (B), but wherein Im represents an imidazolyl group of formula:

25



35 wherein R⁵, R⁶ and R⁷ are as defined in EPA 242973, although one of these groups may additionally represent a vinyl group;

R¹ is as defined in EPA 242973, although one of these groups may additionally represent a group selected from -CO₂R¹⁰, -COR¹⁰, -CONR¹⁰R¹¹ or -SO₂R¹⁰ (wherein R¹⁰ and R¹¹ which may be the same or different, each represents a hydrogen atom, a C₁₋₆ alkyl or C₃₋₇ cycloalkyl group, or a phenyl or phenylC₁₋₄ alkyl group, in which the phenyl group is optionally substituted by one or more C₁₋₄ alkyl, C₁₋₄ alkoxy or hydroxy groups or halogen atoms, with the proviso that R¹⁰ does not represent a hydrogen atom when R¹ represents a group -CO₂R¹⁰ or SO₂R¹⁰);

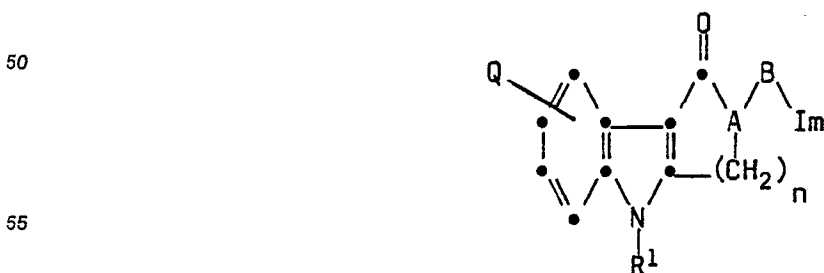
40 R² is as defined in EPA 242973;

A-B represents the group R³R⁴C-CH₂ wherein R³ and R⁴ are as defined in EPA 242973;

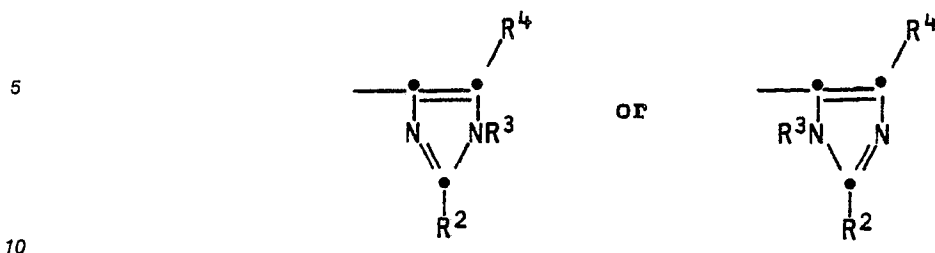
Q is as defined in formula (A);

45 and physiologically acceptable salts and solvates thereof.

British Patent Specification No.2202530A, which was unpublished at the priority date of the present application, discloses compounds of the general formula:



wherein Im represents an imidazolyl group of the formula:



R¹ represents a hydrogen atom or a group selected from C₁₋₆alkyl, C₃₋₆alkenyl, C₃₋₆alkynyl, C₆₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, phenyl, phenylC₁₋₃alkyl, -CO₂R⁵, -COR⁵, -CONR⁵R⁶ or -SO₂R⁵ - (wherein R⁵ and R⁶, which may be the same or different, each represents a hydrogen atom, a C₁₋₆alkyl or C₃₋₇cycloalkyl group, or a phenyl or phenylC₁₋₄alkyl group, in which the phenyl group is optionally substituted by one or more C₁₋₄alkyl, C₁₋₄alkoxy or hydroxy groups or halogen atoms, with the proviso that R⁵ does not represent a hydrogen atom when R¹ represents a group -CO₂R⁵ or -SO₂R⁵);

one of the groups represented by R², R³ and R⁴ is a hydrogen atom or a C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₆alkenyl, phenyl or phenylC₁₋₃alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆alkyl group;

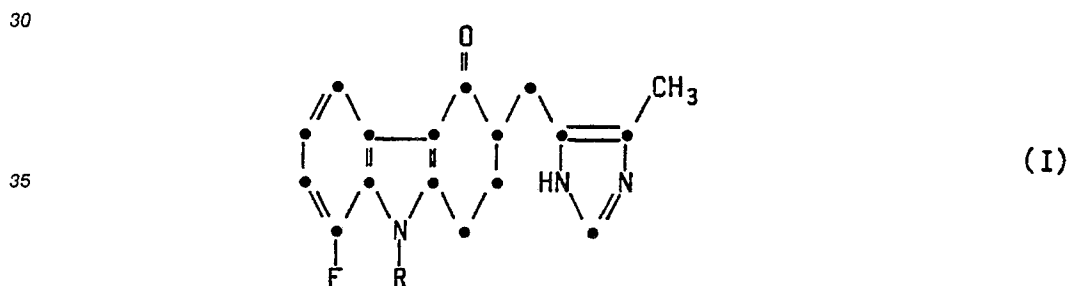
Q is as defined in formula (A);

n represents 1, 2 or 3;

and A-B represents the group CH-CH₂ or C=CH; and physiologically acceptable salts and solvates thereof.

We have now found a novel group of compounds, which although generically covered by the compound definition in GB2202530A, are not specifically disclosed therein, and which are also potent antagonists of the effect of 5-HT at 5-HT₃ receptors. Furthermore the compounds of the present invention have a surprisingly advantageous duration of action.

Thus, the present invention provides a tricyclic ketone of the general formula (I):



wherein R represents a hydrogen atom or a C₁₋₃alkyl (e.g. methyl) group; and physiologically acceptable salts and solvates thereof.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts formed with organic or inorganic acids for example, hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates. The solvates may, for example, be hydrates.

It will be appreciated that the carbon atom at the 3-position of the tetrahydrocarbazolone ring is asymmetric and may exist in the R- or S- configuration. All optical isomers of compounds of general formula (I) and their mixtures including the racemic mixtures thereof, are embraced by the invention.

Referring to the general formula (I), the alkyl group represented by R may be a straight chain or branched chain alkyl group, for example, methyl, ethyl, propyl or prop-2-yl, most preferably methyl.

A particularly preferred compound according to the invention is:

8-fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one and its physiologically acceptable salts and solvates.

A further preferred compound according to the invention is:

8-fluoro-1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one and its physiologically acceptable salts and solvates.

The potent and selective antagonism of 5-HT at 5-HT₃ receptors by compounds of the invention has

been demonstrated by their ability to inhibit 3-(5-methyl-1H-imidazol-4-yl)-1-[1-(methyl- t_3)-1H-indol-3-yl]-1-propanone binding in rat entorhinal cortex homogenates (following the general procedure described by G. Kilpatrick et al. in *Nature*, 1987, 330, 746), and/or by their ability to inhibit the 5-HT-induced depolarisation of the rat isolated vagus nerve preparation.

5 Compounds of formula (I), which antagonise the effect of 5-HT at 5-HT₃ receptors, are useful in the treatment of conditions such as psychotic disorders (e.g. schizophrenia and mania); anxiety; and nausea and vomiting, particularly that associated with cancer chemotherapy and radiotherapy. Compounds of formula (I) are also useful in the treatment of gastric stasis; symptoms of gastrointestinal dysfunction such as occur with dyspepsia, peptic ulcer, reflux oesophagitis, flatulence and irritable bowel syndrome; migraine; and pain. Compounds of formula (I) may also be used in the treatment of dependency on drugs and substances of abuse, depression, and dementia and other cognitive disorders.

According to another aspect, the invention provides a method of treatment of a human or animal subject suffering from a psychotic disorder such as schizophrenia or mania; or from anxiety; nausea or vomiting; gastric stasis; symptoms of gastrointestinal dysfunction such as dyspepsia, reflux oesophagitis, peptic ulcer, 15 flatulence and irritable bowel syndrome; migraine; pain; dependency on drugs and substances of abuse; depression; or dementia or another cognitive disorder, which comprises administering an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound selected from compounds of the general formula (I), and their physiologically acceptable salts and solvates (e.g. hydrates), for use in human or veterinary medicine, and formulated for administration by 20 any convenient route.

Such compositions may be formulated in conventional manner using one or more physiologically acceptable carriers and/or excipients.

Thus the compounds according to the invention may be formulated for oral, buccal, parenteral or rectal 25 administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. 30 lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycolate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid 35 preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

40 Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or 45 continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

50 The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for 55 example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

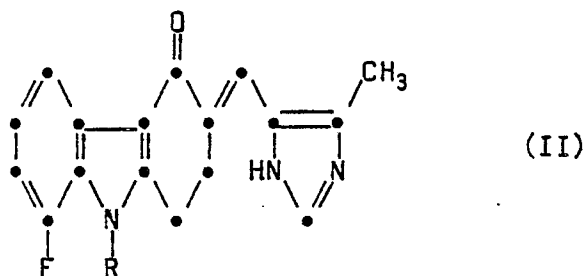
For intranasal administration, the compounds according to the invention may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

The compounds of formula (I) may also be administered in combination with other therapeutic agents. Thus, for example, in the treatment of gastric stasis, symptoms of gastrointestinal dysfunction and nausea and vomiting, the compounds of formula (I) may be administered in combination with antisecretory agents such as histamine H_2 -receptor antagonists (e.g. ranitidine, sufofodine, 1-methyl-5-[[3-[3-(1-piperidinylmethyl)-phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol, cimetidine, famotidine, nizatidine or roxatidine) or H^+K^+ ATPase inhibitors (e.g. omeprazole). In the treatment of nausea and vomiting, compounds of formula (I) may also be administered in combination with dexamethasone.

A proposed dose of the compounds of the invention for administration to man (of approximately 70kg body weight) is 0.001 to 100mg, preferably 0.01 to 50g, more preferably 0.1 to 20mg of the active ingredient per unit dose expressed as the weight of free base, which could be administered, for example, 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient. The dosage will also depend on the route of administration.

According to another aspect of the invention, compounds of general formula (I), and physiologically acceptable salts or solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the group R is as defined for compounds of general formula (I) unless otherwise stated.

According to a first general process (A), a compound of formula (I) may be prepared by hydrogenation of a compound of formula (II):



or a protected derivative thereof, followed where necessary by removal of any protecting groups.

Hydrogenation according to general process (A) may be effected using conventional procedures, for example using hydrogen in the presence of a noble metal catalyst (e.g. palladium, Raney nickel, platinum or rhodium). The catalyst may be supported on, for example, charcoal or alumina, or alternatively a homogeneous catalyst such as tris(triphenylphosphine)rhodium chloride may be used. The hydrogenation will generally be effected in a solvent such as an alcohol (e.g. methanol or ethanol), an ether (e.g. dioxan), a halogenated hydrocarbon (e.g. dichloromethane) or an ester (e.g. ethyl acetate) or mixtures thereof, and at a temperature in the range -20 to $+100^\circ\text{C}$, preferably 0 to 50°C .

Compounds of formula (II) are novel compounds and constitute a further aspect of the invention.

According to another process (B), a compound of formula (I) in which R represents a C_{1-3} alkyl group may be prepared by alkylating the compound of formula (I) wherein R represents a hydrogen atom.

The above alkylation reactions may be effected using the appropriate alkylating agent selected from compounds of formula R^1Z , wherein R^1 represents a C_{1-3} alkyl group, and Z represents a leaving atom or group such as a halogen atom (e.g. chlorine, bromine or iodine), an acyloxy group (e.g. trifluoroacetyloxy or acetoxy), or a sulphonyloxy group (e.g. trifluoromethanesulphonyloxy, *p*-toluenesulphonyloxy or methanesulphonyloxy); or a dialkyl sulphate of formula $(R^1)_2SO_4$.

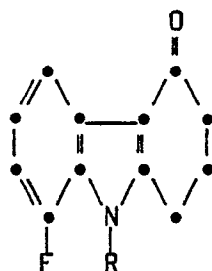
The alkylation reaction is conveniently carried out in an inert organic solvent such as a substituted amide (e.g. dimethylformamide), an ether (e.g. tetrahydrofuran) or an aromatic hydrocarbon (e.g. toluene), preferably in the presence of a base. Suitable bases include, for example, alkali metal hydrides (e.g. sodium hydride), alkali metal amides (e.g. sodium amide or lithium diisopropylamide), alkali metal carbonates (e.g. sodium carbonate) or an alkali metal alkoxide (e.g. sodium or potassium methoxide, ethoxide or t-butoxide). The reaction may conveniently be effected at a temperature in the range -80 to +100°C, preferably -80 to +50°C.

It should be appreciated that in the above transformations it may be necessary or desirable to protect any sensitive groups in the compound in question to avoid undesirable side reactions. For example, it may be necessary to protect the imidazole nitrogen atom, for example with an arylmethyl (e.g. trityl), alkyl (e.g. t-butyl), alkoxymethyl (e.g. methoxymethyl), acyl (e.g. benzyloxycarbonyl) or a sulphonyl (e.g. N,N-dimethylaminosulphonyl or p-toluenesulphonyl) group.

Thus according to another general process (C), a compound of formula (I) may be prepared by the removal of any protecting groups from a protected form of a compound of formula (I). Deprotection may be effected using conventional techniques such as those described in 'Protective Groups in Organic Synthesis' by T. W. Greene (John Wiley and Sons, 1981).

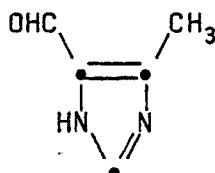
For example, a trityl group may be cleaved by acid hydrolysis (e.g. using dilute hydrochloric or acetic acid). An alkoxyalkyl group may be removed using a Lewis acid such as boron tribromide. An acyl group may be removed by hydrolysis under acidic or basic conditions (e.g. using hydrogen bromide or sodium hydroxide). A sulphonyl group may be removed by alkaline hydrolysis.

Compounds of formula (II) may be prepared by condensing a compound of formula (III):



(III)

with the compound of formula (IV):



(IV)

or a protected derivative thereof, in the presence of a base such as an alkali metal amide (e.g. lithium diisopropylamide) in an inert solvent such as an ether (e.g. tetrahydrofuran), followed by dehydration. The dehydration process may be effected using conventional methods, for example by using an organic or mineral acid (e.g. p-toluenesulphonic, methanesulphonic, trifluoroacetic or hydrochloric acid) in a suitable solvent such as an ether (e.g. tetrahydrofuran), an alcohol (e.g. methanol), or glacial acetic acid, at a temperature in the range 0 to 100°C.

Compounds of formula (III) may be prepared, for example, by the method or methods analogous to that described by H. Iida et al. in *J. Org. Chem.*, 1980, 45, 2938.

The compound of formula (IV) and protected derivatives thereof may be prepared, for example, by the method described in published European Patent Specification No. 242973A.

Where it is desired to isolate a compound of the invention as a salt, for example a physiologically acceptable salt, this may be achieved by reacting the compound of formula (I) in the form of the free base with an appropriate acid, preferably with an equivalent amount, in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an aqueous alcohol (e.g. aqueous ethanol), an ester (e.g. ethyl acetate) or an ether (e.g. tetrahydrofuran).

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compound of formula (I) using conventional methods.

Individual enantiomers of the compounds of the invention may be obtained by resolution of a mixture of enantiomers (e.g. a racemic mixture) using conventional means, such as an optically active resolving acid; see for example 'Stereochemistry of Carbon Compounds' by E.L.Eliel (McGraw Hill, 1962) and 'Tables of Resolving Agents' by S. H. Wilen.

The methods described above for preparing the compounds of the invention may be used for the introduction of the desired groups at any stage in the stepwise formation of the required compounds, and it will be appreciated that these methods can be combined in different ways in such multi-stage processes. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product.

The invention is further illustrated by the following Examples. All temperatures are in °C. Thin layer chromatography (t.l.c.) was carried out on silica, and flash column chromatography (FCC) on silica (Merck 9385). Solvent System A as used for chromatography denotes dichloromethane:ethanol:0.88 ammonia solution. Organic extracts were dried over magnesium sulphate. The following abbreviations are used: THF - tetrahydrofuran; DMF - dimethylformamide.

Intermediate 1

3-[(2-Fluorophenyl)amino]-2-cyclohexen-1-one

2-Fluoroaniline (10g) and cyclohexane-1,3-dione (10g) were heated together under nitrogen at 120° for 1h. The cooled mixture was triturated with ether and filtered to give the title compound (14.8g), m.p. 116-118°.

Intermediate 2

8-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one

3-[(2-Fluorophenyl)amino]-2-cyclohexen-1-one (14.8g), palladium (II) acetate (1g), and copper (II) acetate (29.5g) were heated together in DMF (100ml) under nitrogen at 140° for 2h. The solvent was removed in vacuo, and the residue was purified by FCC eluting with ether to give the title compound (10.1g), m.p. 222-224°.

Intermediate 3

8-Fluoro-1-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

To a suspension of sodium hydride (80% dispersion in oil; 1.15g) in dry THF (50ml) under nitrogen was added 8-fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (6.5g) in dry THF (50ml), and the mixture was stirred for 1h. Methyl iodide (4.1ml) was added, and the mixture was stirred for 3h. The mixture was then poured into brine (300ml) and extracted with ether (2x300ml). The combined, dried organic extracts were evaporated in vacuo to give the title compound (5.77g), m.p. 126-128°.

Intermediate 4

8-Fluoro-1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methylene]-4H-carbazol-4-one

Diisopropylamine (3.83ml) in dry THF (20ml) was cooled to 0° under nitrogen. *n*-Butyllithium (1.69M solution in hexane; 16.3ml) was added, and the mixture was stirred for 15 min. before cooling to -78°. 8-

fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (2.32g) in dry THF (40ml) was cooled to -78° under nitrogen, the lithium diisopropylamide solution was added, and the resulting suspension was stirred for 1h. 5-Methyl-1-(triphenylmethyl)-1H-imidazole-4-carboxaldehyde (4.02g) in dry THF (40ml) was added, and the mixture was stirred at -78° for 1h, then warmed to 20° and stirred for 3h. Methanesulphonic acid (20ml) and acetic acid (30ml) were added, and the mixture was heated to 80° for 1h. The cooled mixture was poured into aqueous potassium carbonate solution (500ml) and extracted with ethyl acetate (3x50ml). The combined, dried organic extracts were evaporated in vacuo to leave an oil which was purified by FCC eluting with System A (75:8:1) to give the title compound (723mg), m.p. 235-237° (decomp.).

10

Intermediate 58-Fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methylene]-4H-carbazol-4-one

15

Diisopropylamine (2.35ml) in dry THF (15ml) was cooled to 0° under nitrogen. n-Butyllithium (1.24M solution in hexane; 13.4ml) was added, and the mixture was stirred for 10 min. before cooling to -78°. 8-fluoro-1-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (3g) in dry THF (70ml) was cooled to -78° under nitrogen, the lithium diisopropylamide solution was added, and the resulting mixture was warmed to -40° over 1h, before re-cooling to -78°. 5-Methyl-1-(triphenylmethyl)-1H-imidazole-4-carboxaldehyde (4.9g) in dry THF (50ml) was added slowly, and the mixture was allowed to warm to 0° over 3h. The mixture was re-cooled to -78°, acetic acid (20ml) was added, followed by methanesulphonic acid (50ml), and the mixture was warmed to 20° and then heated at reflux for 12h. The cooled mixture was poured into water (400ml), basified (to pH10) with potassium carbonate (50g) and extracted with ethyl acetate (3x400ml). The combined, dried organic extracts were evaporated in vacuo to give an oil which was purified by FCC eluting with System A (100:8:1) to give the title compound (2.79g), m.p. 260-264° (decomp.).

25

Example 1

30

8-Fluoro-1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one

8-Fluoro-1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methylene]-4H-carbazol-4-one (728mg) in absolute ethanol (30ml) was added to a suspension of 5% palladium on charcoal (100mg) in ethanol (30ml), and the resulting mixture was hydrogenated at room temperature and atmospheric pressure until hydrogen uptake had ceased. The mixture was filtered, and the filtrate was evaporated in vacuo to leave an oil which was purified by FCC eluting with ethanol: ethyl acetate (1:5) to give the title compound (342mg), m.p. 135-140°, t.l.c. (ethanol:ethyl acetate, 1:5) Rf 0.175.

40

Example 28-Fluoro-1, 2, 3, 9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one

8-Fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methylene]-4H-carbazol-4-one (1.5g) was dissolved in ethanol (50ml) and added to a suspension of 5% palladium on charcoal (200mg) in ethanol (ca. 50ml), and the resulting mixture was hydrogenated at room temperature and atmospheric pressure until hydrogen uptake had ceased. The mixture was filtered, and the filtrate was evaporated in vacuo to give the title compound (1.5g), m.p. 189-191° (decomp.), t.l.c. (System A 100:8:1), Rf 0.43.

55

Example 38-Fluoro-1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one maleate

8-Fluoro-1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one (330mg) was dissolved in dry ethanol (20ml). Maleic acid (129mg) in ethanol (10ml) was added, and the solution was evaporated in vacuo. The residue was triturated with ether and the resultant solid was crystallised from ethanol:ether to give the title compound (351mg), m.p. 174-177°.

Analysis Found:	C,60.6;	H,5.0;	N,9.9;
C ₂₁ H ₂₀ FN ₃ O ₅ requires	C,61.0;	H,4.9;	N,10.2%.

Example 4

8-Fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one maleate

8-Fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one (1.51g) was dissolved in ethyl acetate (40ml), and added to a solution of maleic acid (563mg) in ethanol (50ml). The solution was cooled to 0°, and the resultant solid was filtered off and dried in vacuo to give the title compound (1.61g), m.p. 155-158°, t.l.c. (System A 100:8:1), Rf 0.43.

The following examples illustrate pharmaceutical formulations according to the invention, containing 8-fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one as the active ingredient. Physiologically acceptable salts and/or solvates of this compound, and other compounds of formula (I) and their physiologically acceptable salts and/or solvates may be formulated in a similar manner.

TABLETS FOR ORAL ADMINISTRATION

Tablets may be prepared by the normal methods such as direct compression or wet granulation.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Direct Compression

Tablet	mg/tablet
Active Ingredient	0.50
Calcium Hydrogen Phosphate BP*	87.25
Croscarmellose Sodium NF	1.80
Magnesium Stearate BP	0.45
Compression weight	90.00

* of a grade suitable for direct compression.

The active ingredient is passed through a 60 mesh sieve, blended with the calcium hydrogen phosphate, croscarmellose sodium and magnesium stearate. The resultant mix is compressed into tablets using a Manesty F3 tablet machine fitted with 5.5mm, flat bevelled edge punches.

CAPSULES	mg/tablet
Active Ingredient	0.5
* Starch 1500	98.5
Magnesium Stearate BP	1.0
Fill Weight	100.0

* a form of directly compressible starch.

- 10 The active ingredient is sieved and blended with the excipients. The mix is filled into size No. 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary changing the capsule size to suit.

15 SYRUP

This may be either a sucrose or sucrose free presentation.

Sucrose-Free	mg/5ml dose
Active Ingredient	0.5
Hydroxypropylmethylcellulose USP (viscosity type 4000)	22.5
Buffer)	as required
Flavour)	
Colour)	
Preservative)	
Sweetener)	5.0ml
Purified Water BP to	

- 30 The hydroxypropylmethylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

35 INJECTION FOR INTRAVENOUS ADMINISTRATION

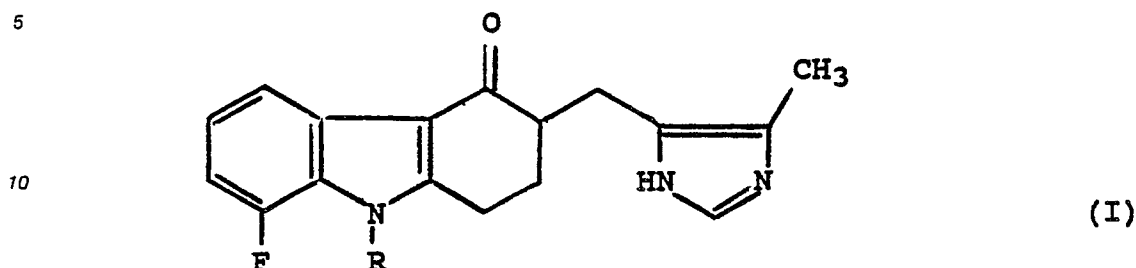
	mg/ml	
Active ingredient	0.05	0.5
Sodium Chloride BP	as required	as required
Water for Injection BP to	1.0ml	1.0ml

- 45 Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or facilitate solution of the active ingredient. Alternatively, suitable buffer salts may be used.

- 50 The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively, the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

Claims

1. Compounds of the general formula (I)



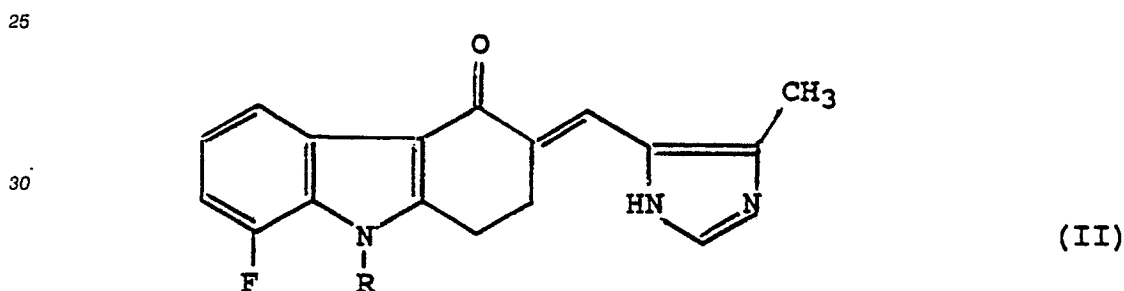
15 wherein R represents a hydrogen atom or a C₁₋₃alkyl group and physiologically acceptable salts and solvates thereof.

2. 8-fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one and physiologically acceptable salts and solvates thereof.

20 3. 8-fluoro-1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one and physiologically acceptable salts and solvates thereof.

4. A process for the preparation of compounds as claimed in any of claims 1 to 3 and physiologically acceptable salts and solvates thereof which comprises:

(A) hydrogenating a compound of formula (II)



35 or a protected derivative thereof, followed where necessary by removal of any protecting group(s) present; or

(B) for the preparation of a compound of formula (I) in which R represents a C₁₋₃alkyl group, alkylating the compound of formula (I) in which R represents a hydrogen atom; or

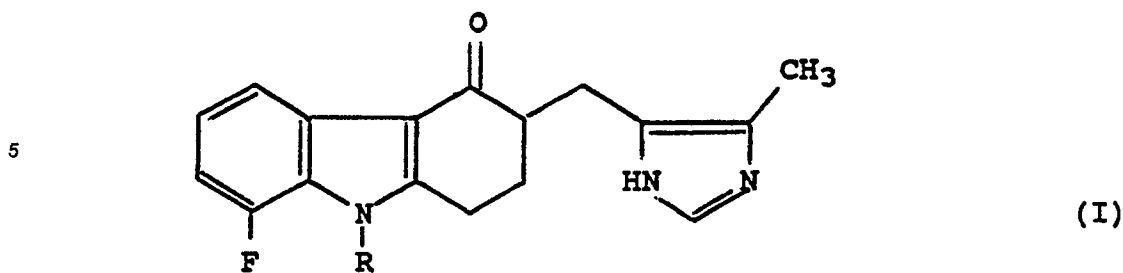
40 (C) removing one or more protecting groups from a protected form of a compound of formula (I) and when the compound of formula (I) is obtained as a mixture of enantiomers, optionally resolving the mixture to obtain the desired enantiomer; and/or where the compound of formula (I) is in the form of a free base, optionally converting the free base into a salt.

45 5. A pharmaceutical composition comprising a compound, of general formula (I) as defined in any of Claims 1 to 3 or a physiologically acceptable salt or solvate thereof together with at least one physiologically acceptable carrier or excipient.

50 6. A compound of general formula (I) as defined in any of Claims 1 to 3 or a physiologically acceptable salt or solvate thereof for use as an active therapeutic agent.

CLAIMS FOR THE FOLLOWING CONTRACTING STATES: GR, ES.

55 1. A process for the preparation of compounds of the general formula (I)

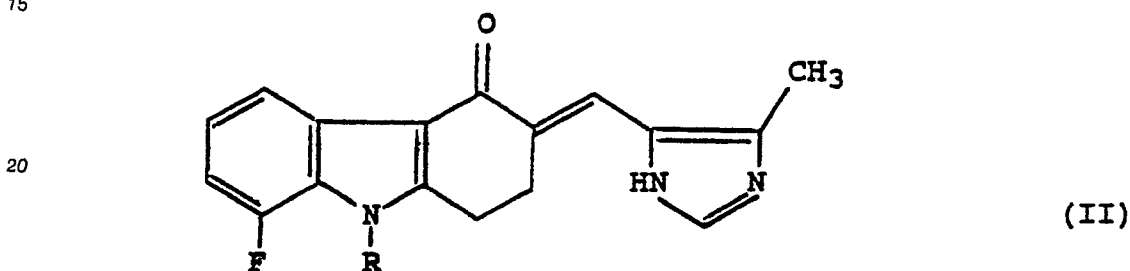


10

wherein R represents a hydrogen atom or a C₁₋₃alkyl group and physiologically acceptable salts and solvates thereof, which comprises:

(A) hydrogenating a compound of formula (II)

15



25

or a protected derivative thereof, followed where necessary by removal of any protecting group(s) present; or

(B) for the preparation of a compound of formula (I) in which R represents a C₁₋₃alkyl group, alkylating the compound of formula (I) in which R represents a hydrogen atom; or

30

(C) removing one or more protecting groups from a protected form of a compound of formula (I); and when the compound of formula (I) is obtained as a mixture of enantiomers, optionally resolving the mixture to obtain the desired enantiomer; and/or

where the compound of formula (I) is in the form of a free base, optionally converting the free base into a salt.

35

2. A process as claimed in claim 1 for the preparation of the compound:

8-fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one or a physiologically acceptable salt or solvate thereof.

40

3. A process as claimed in claim 1 for the preparation of the compound: 8-fluoro-1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one or a physiologically acceptable salt or solvate thereof.

45

50

55



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A,D	EP-A-0 242 973 (GLAXO GROUP LIMITED) * claims 1,10,11 * ---	1,4-6	C 07 D 403/06 A 61 K 31/415// C 07 C 119/12
P,A	DE-A-3 740 352 (GLAXO GROUP LTD.) * claims 1,17,18,21-29 *; & GB - A - 2202530 (Cat. D) ---	1,4-6	
P,A	EP-A-0 307 145 (GLAXO GROUP LTD.) * claims 1-3,5,7,10,11 * -----	1,4-6	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 D 403/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 31-07-1989	Examiner VAN AMSTERDAM L.J.P.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	